Comparison of Neostigmin Versus Sugammadex in Reversal of Neuromuscular Blockade after Abdominal Surgery of Obese Patients Whose Bmi ≥30

Batın Cerrahisi Uygulanan BMI≥30 Üzerinde olan Obez Hastalarda Nöromuskuler Bloğun Geri Döndürülmesinde Neostigmin ve Sugammadeksin Karşılaştırılması

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Abstract: Our aim is to compare neostigmin versus sugammadex in reversal of neuromuscular blockade of vecu-ronium after abdominal surgery of obese patients whose BMI ≥30. This study is performed on 70 patients whose BMI ≥30 and ASA I-II-III. They are 18-65 years old and scheduled for any abdominal surgery under general anesthesia. They are monitorized with TOF-watch for neuromuscular blockade and standard non-invasive monitorization. Vecuronium 0,1 mg/kg is given during anesthesia induction. According to type of surgery, extra doses of vecuronium 0.01-0.02 mg/kg is added to keep TOF between 0-2. During recovery period, when TOF number exceeds 2 and diaphragmatic movements begin, group sug received sugammadex 2 mg/kg and group neo received neostigmin 0,05 mg/kg with atropine 0,02 mg/kg. When TOF ratio becomes 0,9 and clinical evaluation is completed, patient is extubed. Group sug and neo recovery durations from TOF2 to TOF 0.9 are respectively 3,7 minutes and 14 minutes. (p<0,001) Demographic data revealed no significant difference between Group sug and group neo except BMI and surgery type (p=0,017 , p=0,008). PORC(Postoperative residual curarization) is a predicted complication in obesity. Sugammadex is superior than neostigmine especially in obese critical patients in terms of effective faster and safer airway management.
Key Words: sugammadex, neostigmine, obesity, anesthesia

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Özet: Bu çalışmadaki amacımız BMI≥30 üzerindeki obez hastalarda , batın cerrahisi operasyonlarında, vekuronyum ile sağlanan nöromüsküler bloğun geri döndürülmesinde neostigmin ve sugammadeksin etkinliğinin karşılaştırılmasıdır. Bu çalışma genel anestezi altında, batın cerrahisi planlanan, ASA I-II-III olan, 18-65 yaş arası, BMI≥30 üzerindeki 70 hastada yapıldı. Noninvaziv monitorizasyonla birlikte nöromuskuler monitorizasyon için TOF - Watch uygulandı. Anestezi indüksiyonunda kas gevşetici olarak vekuronyum 0.1 mg/kg uygulandı, cerrahinin türüne göre TOF 0-2 arasında olacak şekilde 0.01 -0.02 (mg/kg) vekuronyum ile ek doz uygulandı. Derlenme döneminde TOF sayısının 2 nin üzerinde ve klinik olarak diyafram haraketlerinin başladıktan sonra nöromuskuler bloğun geri döndürülmesinde sugammadeks (grup sug) 2mg/kg ve neostigmin (grup neo) 0.05mg/kg ile birlikte atropin 0.02mg/kg uygulandı . TOF oranı 0.9 olduğunda ve hastanın klinik değerlendirilmesi sonucu extübe edildi. Grup sug ve neo hastalarda T2'den TOF oranı 0.9'a ulaşma süresi sırasıyla 3,7 dk ve 14 dk idi (p<0,001). Demografik verilerde Grup sug ve grup neo arasında BMI ve ameliyat türü dışında anlamlı fark bulunmadı (p=0,017 , p=0,008). PORC obezitede öngörülebilir bir komplikasyondur. Sugammadeks, neostigmine göre obezite gibi kritik hastalarda daha hızlı ve güvenli hava yolu sağlamada etkin bir ajan olduğunu düşünmekteyiz.
Anahtar Kelimeler: sugammadeks, neostigmin, obezite ,anestezi

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1. Introduction

The components of general anesthesia are loss of consciousness, analgesia and muscle relaxation. Muscle relaxation is indicated for optimisation of surgical conditions, fascilitation of endotracheal intubation during operations (1,2,3).

Definition of postoperative residual curarisation is; "presence of signs and symptoms of postoperative muscle weakness after intraoperative nondepolarizing neuromuscular blocker" which means presence of nicotinic receptors (4). PORC (postoperative residual curarisation) overall incidence is 60% after general anesthesia. This incidence is increased especially in olderly and/or obese patients with co- morbidities. During residual block, the chemoreceptor response against hypoxia is decreased. Larengeal and pharengeal reflexes are depressed which may lead to regurgitation and aspiration risk (5).

PORC is a very important factor which increases morbidity and mortality during post-operative period. Residual block risk decreases if medium-acting neuromuscular blockers are preferred, in addition neuromuscular monitors are also useful in reversal of block. In clinical practice, TOF ratio 0.9 is golden standard in order to rule out residual block (6).

For reversal of non-depolarising NMBA (neuromuscular block antagonist), acetyl-cholinesterase inhibitors (for example neostigmine) are used. Ach-esterase inhibitors prevent degradation of Ach and neuromuscular transmission is provided again. However, Ach-esterase inhibitors act both on nicotinic receptors and muscarinic receptors which are responsible from muscarinic side effects. (bradycardia, hypotension, bronchoconstriction, hypersalivation, nausea-vomit) (7). Sugammadex© is rocuronium-specific new generation neuromuscular block antagonist; with modified cyclodextrin structure which is effective against aminosteroid structure relaxants (especially rocuronium). (8,9,10) NMBA is effected via encapsulation way. There is no receptor level interaction so that there is no muscarinic side effect. During deep block, Sugammadex© is more advantageous over neostigmine, because of its faster onset of action and way of interaction (7,11). Obesity and especially morbid obesity may lead to life threatening anesthetic problems, difficult intubation, hypoventilation and prolonged neuromuscular blockade (12). Neuromuscular blockers have variable distribution and metabolic half-life. Hence, this variability may increase the incidence of prolonged neuromuscular blockade (13). This study is conducted on obese patients undergoing elective surgery under general anesthesia. Vecuronium is used as neuromuscular blocker. We compared neostigmine versus sugammadex in reversal of neuromuscular block.

2. Materials and Method

This study is approved by Eskişehir Osmangazi University Faculty of Medicine Anesthesiology and Reanimation Department, Ethical Committee 23.10.2013 date and 03 number. This study is conducted on total 70 obese patients whose BMI ≥30 aged between 18-65 years, undergoing elective surgery under general anesthesia. After informed consent, ASA I-II-III group patients are included. Exclusion criteria as follows; neuromuscular block is affected by some drugs (for example some antibiotics, anticonvulsants and magnesium); obvious or suspected renal dysfunction; hepatic dysfunction; malign hyperthermia history; opioids, neuromuscular blockers and some other drugs which are used during general anesthesia. Some conditions where neostigmine or atropine is contra-indicated like pregnancy or lactation are also excluded.

Before induction of general anesthesia, % 0.9 serum physiologicis given via intravenous line (fluid replacement according to surgery).

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR) and cardiac rythm recording (ECG), peripheric oxygen saturations (Sp02), neuromuscular monitor with TOF-Watch (Organon Technika, Boxtel, Holland) are preferred. Nerve stimulator is activated after induction, when consciousness is lost.

In order to reach supra-maximal stimulation, skin is cleaned with alcohol. For ulnar nerve stimulation on proximal volar side of wrist, stimulator electrodes are placed along ulnar nerve track in order to get highest current density. Temperature probe is fixed to the tenar area. Skin temperature is kept between 32-34 ° celcius. Acceleration transducer is placed on plantar surface of thumb which evaluates adduction response against ulnar nerve stimulus.Anesthesia induction is intravenous thiopental sodium (3-6mg/kg) andremifentanyl 1 mcg/kg. Anesthesia maintenance is sevoflorane % 2-3 , %50 oxygen and %50 N2O. Neuromuscular monitor involved calibration with supra-maximal stimulus. During search for supra-maximal threshold value, 1 Hertz or 0.1 Hertz single stimulus is preferred and stimulation mode is changed to TOF. After the response is taken against stimulus, vecuronium 0.1 mg/kg is administered bolus intravenously. When TOF responses are completely lost (TOF number is 0-zero), tracheal intubation is performed. If TOF stimulation is one or two, muscle relaxation will be adequate, so that most surgical operations can be performed without any problems. During surgical period, TOF number is kept between 0-zero and two; as such additional vecuronium 0.01 -0.02 mg/kg is administered bolus intravenously according to patients' clinical status and type of surgery itself.

During recovery period, we waited until TOF number is two or more, beginning of clinically obvious diaphragmatic movements and then we administered neuromuscular reversal agents. Group sug received sugammadex 2 mg/kg (Bridion, MSD, Oss, The Netherlands). Group neo received neostigmin 0.05mg /kg with atropin 0.02mg/kg. When TOF ratio reached ≥0.9 and patient is clinically stable, extubation is performed. (Drug onset of action (T0), drug action duration (T1), additional dose duration (T2) and recovery durations (TOF2-TOF 0,9))Vecuronium is administered and onset of action (time until intubation), duration of action (time until first TOF number appears), additional dose requirement during surgery, recovery durations (when TOF number is over 2 and reversal agents are administered, then TOF ratio becomes 0.9 and extubation is performed after clinical evaluation). Continuous quantitative data is expressed as n, average and standard deviation. Qualitative data is expressed as n, median value, Q1 and Q3 . Continuous data is composed of independent measurements. Continuous data have normal distribution. Continuous data is analyzed via t test. Variables without normal distribution are analyzed via Mann-Whitney U test. Relationship between variables are shown via normality tests. According to these normality tests, Pearson Correlation tests are applied to variables with normal distribution whereas Spearman Correlation tests are applied to variables without normal distributions. Chi-sqare tests are applied to categoric structure data sets. $p<0.05$ probability value is accepted as significant. All data analyses are performed via SPSS 21.0 packed programs.

3. Results

Study included total 70 patients, undergoing abdominal surgery (laparoscopic (LC) and laparotomy (LT)) whose BMI ≥30 and aged between 18-65 years, ASA I-II-III. Group sug (sugammadeks n=35), group neo (neostigmin n=35) are two groups to be compared. Patients demographic features and anesthesia durations (minute), surgery durations (minute), type of surgery (LC/LT) are shown in table-1.

Table.1
Demographic Features in Group Sug and Neo

Feature	Group sug(n:35)	Group neo (n:35)	p
Age (year)	46 (42-60)	45 (42-53)	0.819
Weight	90 (85-105)	88 (82-97)	0,112
Height	1.59 (1.55-1.66)	1.60 (1,55-1,64)	0.892
BMI (kg/m2)	35 (33-39)	33 (31-35)	0,017*
Anesthesia Durati on (minute)	86 (70-110)	84 (77-100)	0,846
Surgery Duration (minute)	80 (64-104)	74 (66-90)	0,499
ASA class (I/II/ III)	12/21/2	18/16/1	0,412
Sex F/Male (n)	32/3	33/2	>0,05
Type of Surgery (LT/LT)(n)	22/13	10/25	0,008*

M: Male; F: Female; ASA: American Society of Anesthesiologists physical status scale; BMI: Body Mass Index;LC: Laparoscopic;LT:Laparotomy
**Significant difference found.(p<0.05)*

Group sug and group neo revealed no significant difference of BMI and type of surgery (p=0,017 , p=0,008). Drug onset of action (T0), drug action duration (T1), additional dose duration (T2) and recovery durations (TOF2-TOF 0,9) are shown in table-2.

Table.2.
Drug onset of action , drug action duration , additional dose duration and recovery durations groups

Feature	Group sug (n:35)	Group neo (n:35)	p
Onset of action (T0) (minute)	3,36±60,70	3,37±0,58	0,939
Action duration (T1) (minute)	46 ±10,12	41,97 ±7,86	0,067

Additional dose duration (T2) (minute)	55,47 ±13,11	50,71±9,49	0,193
RecoveryDurati on (TOF2-TOF0,9) (minute)	3,7 (3,16-4,16)	14 (9,41-14,6)	0,001*

Drug onset of action (T0), drug action duration (T1), additional dose duration (T2) and recovery durations (TOF2-TOF 0,9)

Group sug ve group neo revealed no significant difference except *recovery durations*. (p<0,001) Group sug and neo *recovery durations* of patients from TOF2 to TOF ratio 0,9 reaching durations are respectively 3,7 minutes versus 14 minutes. This significant different is attributed to sugammadex action.

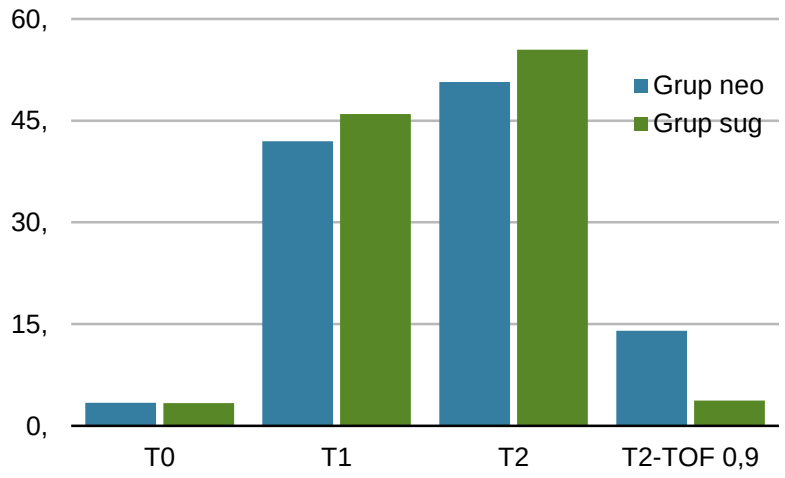

Figure 1.*Drug onset of action (T0), drug action duration (T1), additional dose(T2) and recovery durations (TOF2-TOF 0,9)*

At the same time, Group sug has inside itself important level positive correlation between recovery period and onset of action (p=0,01, r:0,431). Additional dose number is negatively correlated with age and drug half-life (p=0,012, r= -0,419, p=0,021;r:-0,389).

Group neo has inside itself intermediate level positive correlation between recovery period versus weight and BMI (p=0,003; r=0,489, p=0,017; r =0,399). There is important level positive correlation between BMI and additional dose number. There is negative correlation between BMI and drug action duration. (p=0,015; r: 0:408, p=0,024; r: -0,381) There is positive correlation between age and drug onset of action (p=0,032; r:0,363).

There is no correlation of heart rate between groups (p>0.05) (Figure-6). Group neo has heart rate TOF 2: 81, TOF:0,9:86, post-extubation:84 which means there is no statistically significant difference within group (p=0,334). Group sug has heart rate TOF 2:76, TOF 0,9:84, post-extubation:85 which means there is statistically significant difference between TOF 2 with TOF 0,9 and post-extubation (p<0,05).

There is statistically significant difference of SpO_2 between Group sug and Group neo at pre-induction measurements (p=0,027).

There is no statistically significant difference of SBP (systolic blood pressure) between groups (p>0.05).

There is statistically significant difference of DBP (diastolic blood pressure) between

Group sug and Group neo at pre-induction measurements, at fifth minute, at TOF 0,9 and post-extubation diastolic values (p=0,009, p=0,012, p=0,008, p=0,008).

There is statistically significant difference of MBP (mean blood pressure) between

Group sug and Group neo at post-extubation measurment values (p=0,041) At post-anesthetic care unit, patients are monitored for 45 minutes. Clinically, (5 seconds head up position or hand shake, eye opening to verbal stimulus, swallowing, oxygenisation should be SpO_2 ≥95) both groups are followed up in terms of any sign or symptom of residual neuromuscular block. There is no significant residual neuromuscular block which might cause respiratory distress (SpO_2 <90) or any side effect requiring intervention.

4. Discussion

In our study, we compared sugammadex versus neostigmine as reversal agents in obese patients undergoing abdominal surgery using vecuronium as muscle relaxant.

Vecuronium is the medium-acting-neuromuscular blocker. Sugammadex group is found to have significantly faster recovery. The recovery duration of group NEO is found to be associated to BMI (, p=0,017; r =0,399), however group SUG has no significant relation of BMI.

Morbid obese patients have limited vital functions, hence postoperative residual curarisation must be prevented in order to get secure airway and intact respiratory reflexes. After extubation, aspiration risk increases because larengeal/pharengeal reflexes are depressed which may lead to acute respiratory failure (14). NeuroMuscular Block Agents are normally metabolized and eliminated, however there is a very big variability between these agents (4) Murphy et al conducted a study in postanesthetic care unit recovery room and included patients at admission, observed those patients for 15 minutes. CRE (Critical Respiratory Event) incidence is found to be %0,8 . Those CRE are consisted of %52,4 hypoxemia, %35 upper respiratory tract obstruction. TOF ratio of CRE patients are %62, whereas TOF ratio of non-CRE patients are %98. Murphy et al suggests that one of the reasons of CRE is PORC . Mild degree residual paralysis (TOF 0,7- TOF 0,9) may be associated with respiratory and pharengeal muscle dysfunction. Thus, golden standard TOF response is accepted as TOF 0,9 for complete neuromuscular recovery (6) Mild degree residual curarisations increase CRE risk in postanesthetic care unit recovery room. Especially, morbid obese patients are more sensitive to CRE. Carron M et al presented a case report (BMI:51, Weight: 160 kg) where neuromuscular block is provided by rocuronium. This neuromuscular block is reversed by neostigmin 4.5 mg and atropin 0.7 mg when TOF:0,14. After 9 minutes, TOF becomes 0,91 and patient is extubated. However, 30 minutes later, desaturation and muscle weakness have been reported. Then, sugammadex 50 mg is administered and 5 minutes later, clinical condition of the patient is fine. This case report shows that CRE may be seen even after TOF>0,9 . Neostigmine may reverse the neuromuscular block of rocuronium but more side effects are seen, furthermore its effects are too slow especially in morbid obese patients. Because of the "ceiling effect", doses over 5 mg don't have any increasing effect. In conclusion, this study suggests that suggammadex should be preferred if CRE happens in morbid obese patients postoperatively after neostigmine (15). Obesity leads to changes of anesthetic drug pharmacodynamics. Most of the muscle relaxants are hydrophilic. In order to prevent overdose, IBW (ideal body weight) must be

used. Overdose might cause prolonged recovery and post-operative respiratory complications. Vecuronium is a weak-mild lipophilic agent, which distributes into non-lipid tissues as well. Vecuronium is a non-depolarising NMBA and more potent than rocuronium (11,16). Vecuronium block reversal is much slower than similar rocuronium block reversal via sugammadex (17,18). Pühringer F.K. et al conducted a study comparing vecuronium versus rocuronium reversal via sugammadex with increasing doses of 0.5, 1.0, 2.0 and 4.0 mg/kg. Recovery durations TOF 2-TOF 0,9 of rocuronium group are respectively 2 and 4 mg/kg sugammadex to 1.4 and 1.5 minutes. Whereas recovery durations TOF 2-TOF 0,9 of vecuronium group are respectively 2 and 4 mg/kg sugammadex to 3.4 and 3.0 minutes (19). Although sugammadex is effective against aminosteroid structure NMBA, its affinity to rocuronium is much more prominent (20). Gaszynski T. et al conducted a similar study on morbid obese (BMI>40) patient group comparing rocuronium versus vecuronium in reversal of neuromuscular block. According to IBW (ideal body weight), group sug received sugammadex 2mg/kg of IBW, group neo received neostigmin 0,05 mg/kg with atropine 0,02 mg/kg of IBW. The duration from TOF 2 to TOF 0,9 is respectively group SUG: 2 minutes 44 seconds and group NEO: 9 minutes 37 seconds (14). Van Lancker P. et al conducted a study on morbid obese (BMI>40) patient group comparing 4 different sugammadex doses versus each other after neuromuscular block via rocuronium. The duration from TOF 2 to TOF 0,9 is IBW:188 seconds, IBW+%20: 154 seconds, IBW+%40: 112 seconds and RBW: 128 seconds. This study concludes that optimal dose of sugammadex is 2mg/kg IBW+%40 (21). In our study, same drugs with similar doses are administered according to RBW (real body weight) Group sug: 3,7 minutes and Group neo:14 minutes. Total body water is normally %65, however morbid obese have only %40 water. This changes distribution volume of drugs. Hydrophyllic drugs easily become overdose if they are administered according to RBW (16,22). Sugammadex is weak-lipofilik, therefore this pharmacokinetic feature requires to be administered according to IBW or lean body weight. However, it is also safe and effective even when adninistered according to RBW (21,23). Koç F et al conducted a similar study comparing heart rates after administration of neostigmin at O.minute:83 beat/min, 6.th minute:66 beat/min, 10.th minute:65 beat/ minute. The heart rate difference between 0.minute and 6.th minute is significant, which means heart rate decreased significantly but it is clinically within optimal boundaries. The reason is thought to be because atropine and neostigmin are administered together or anesthetic depth is affected by some other variables or post-operative pain may accompany at this time period (4). Woo T. et al conducted a study comparing sugammadex 2 mg/kg versus neostigmine 0,05mg/kg-10mcg/kg glykopyrolate in reversal of rocuronium block; they concluded that there is no significant difference between groups in terms of SBP, DBP, MBP and HR (24). In our study, there is no significant difference between groups in terms of HR. Group NEO received neostigmin and atropin simultaneously; TOF 2:81beat/minute, TOF:0,9:86 beat/minute, post-extubation:84 beat/minute. HR has no significant difference between groups (p=0,334). Group SUG has TOF 2:78beat/minute, TOF 0,9: 88beat/minute, post-extubation:86beat/minute. There is significant difference between groups in terms of TOF 2 versus TOF 0,9 and post-extubation heart rates (p=<0,001, p= 0,011). The reason of this significant difference is attributed to the hemodynamic changes during recovery period.

Khuenl-Brady K. S. et al conducted a similar study comparing neostigmine versus sugammadex in reversal of vecuronium block. Recovery period (TOF2-TOF0,9) of neostigmin is 17,9 minutes and sugammadex 2,7 minutes. Single induction dose neuromuscular blockers have recovery period of sugammadeks 2,3 minutes and neostigmine 15,9 minutes. Repeating doses of neuromuscular blockers have recovery period of sugammadex 3,5 minutes and neostigmine 28 minutes. Statistical analyses

could not be performed because the total number of patients are too small (17). In our study, recovery period (TOF2-TOF 0,9) is respectively Group Sug average is 3,7 minutes and Group Neo is 14 minutes. The relationship between recovery period and repeating doses revealed negative correlation for Group Sug and positive correlation for Group Neo.

Vecuronium has polar and hydrophilic structure. If it is administered according to RBW, it may cause overdose reactions (18). TSuzuki et al conducted a study comparing normal (18,5<BMI<25), overweight (25<BMI<30) versus obese (BMI>30) patients whose vecuronium dose were administered according to RBW. They found that obese and overweight patients have faster onset and longer action of vecuronium. After adequate TOF response, neostigmin 0,04 mg with 0,02mg/kg atropin are administered. Time to reach TOF 0,5 and TOF 0,7 are similar between groups. However, time to reach TOF 0,9 is much longer obese and overweight patients than normal weight patients. Likewise, in our study, according to RBW, Group NEO has positive corelation between BMI and drug action duration. If BMI increases, recovery period also increases. Non depolarising NMBA doses should be adjusted to IBW in obese patients to prevent overdose, as such the effects would be similar to normal weight patients (13). Both studies show that neostigmin action duration increases if BMI increases. Sugammadex causes rarely cardiovascular side effects (hypotension, hypertension, lengthened QT interval), mild cough, fever, allergy, nausea-vomit, constipation, taste feeling changes during higher doses (25). This study aims to evaluate PORC clinically in postanesthetic care unit recovery room. Head tilt for 5 seconds, hand shake, eye opening to verbal contact, swallowing, SpO2 ≥95 are the parameters to be evaluated. There was no any sign of residual neuromuscular block in postanesthetic care unit recovery room which might cause respiratory distress (SpO2<90). Nevertheless, sugammadex is a new drug, so its side effects should be investigated in further studies in terms of residual curarisation.

5. Conclusion

Obesity causes some physiological changes which may lead to distorted pharmacodynamics of some drugs, especially NMBA have hydrophilic structure which causes earlier onset of action and longer action duration. Obese patients have longer recovery periods and increased incidence of PORC and/or CRE. In order to prevent PORC, short and medium acting agents should be preferred, intraoperative neuromuscular monitorisation should be performed, reversal agents should be routinely used. We compared sugammadex versus neostigmine in obese patients who are especially at risk of PORC after vecuronium block. Our results are similar to other studies where sugammadex is superior than neostigmine in obese patients in terms of effective faster action and safer airway management.

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